



**University of
Zurich^{UZH}**

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2013

Functional brain maturation assessed during early life correlates with anatomical brain maturation at term-equivalent age in preterm infants

Natalucci, Giancarlo ; Leuchter, Russia Ha-Vinh ; Bucher, Hans Ulrich ; Latal, Beatrice ; Koller, Brigitte ; Hüppi, Petra S ; Hagmann, Cornelia

Abstract: Background: Amplitude-integrated electroencephalogram (aEEG) is a reliable monitoring tool for electrocortical activity with good predictive value in preterm infants. Magnetic resonance imaging (MRI) is a good neuroimaging tool to detect brain lesions and to evaluate brain maturation. We hypothesized that early aEEG measures, recorded over the first 3 d of life in very preterm infants, correlate with brain maturation and injury score assessed by conventional MRI at term-equivalent age. **Methods:** Thirty-nine infants born at a mean (range) gestational age (GA) of 29.5 (27.0-31.9) wk and birth weight 1,230 (680-2,020) g had continuous aEEG during the first postnatal 72-84 h. aEEG maturity scores and average maximum and minimum amplitudes were evaluated. Conventional brain MRI was performed at 41.2 (37.1-44.1) wk postmenstrual age (PMA) on a 3T GE system and scored qualitatively for injury and maturation. **Results:** The average aEEG total maturity score and its cycling subscore were positively and significantly associated with the total MRI maturation score after adjustment for GA, morphine sedation, and PMA at MRI examination. No association was found between the aEEG measures and the MRI injury scores. **Conclusion:** Early aEEG maturity seems to relate to structural MRI brain maturation at term-equivalent age in preterm infants.

DOI: <https://doi.org/10.1038/pr.2013.57>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-79558>

Journal Article

Accepted Version

Originally published at:

Natalucci, Giancarlo; Leuchter, Russia Ha-Vinh; Bucher, Hans Ulrich; Latal, Beatrice; Koller, Brigitte; Hüppi, Petra S; Hagmann, Cornelia (2013). Functional brain maturation assessed during early life correlates with anatomical brain maturation at term-equivalent age in preterm infants. *Pediatric Research*, 74(1):68-74.

DOI: <https://doi.org/10.1038/pr.2013.57>

Functional brain maturation assessed during early life correlates with anatomical brain maturation at term equivalent age in preterm infants.

Running title

Brain maturation on aEEG and MRI.

Authors

Giancarlo Natalucci^{1,2,*}, Russia Ha-Vinh Leuchter³, Hans Ulrich Bucher¹, Beatrice Latal^{1,2}, Brigitte Koller¹, Petra S. Hüppi³, Cornelia Hagmann¹

Affiliations

¹Department of Neonatology, University Hospital Zurich, 8091 Zurich, Switzerland

²Child Development Center, University Children's Hospital, Zurich, Switzerland

³Division of Child Growth & Development, University of Geneva, Geneva, Switzerland.

***Corresponding author**

Giancarlo Natalucci, MD; Department of Neonatology, University Hospital Zurich; 8091 Zurich, Switzerland; Tel: +41-44-2555386; Fax: +41-44-2554442; e-mail: Giancarlo.nataluccil@usz.ch

Funding

Giancarlo Natalucci (GN) and Russia Ha-Vinh Leuchter (RHL) were funded by the Swiss National Science Foundation; grant 33CM30-124101. Cornelia Hagmann (CH) was funded by the Swiss National Foundation Marie-Heim Vögtlin; grant PMPDP3_129104. All authors declare no actual or potential conflict of interest.

Category of study

Clinical study

ABSTRACT

Background: Amplitude-integrated electroencephalogram (aEEG) is a reliable monitoring tool for electro-cortical activity with good predictive value in preterm infants. Magnetic resonance imaging is a good neuroimaging tool to detect brain lesions and to evaluate brain maturation. We hypothesized that early aEEG measures, recorded over the first three days of life in very preterm infants correlate with brain maturation and injury score assessed by conventional MRI at term equivalent age. **Methods:** 39 infants born at a mean (range) gestational age (GA) of 29.5 (27.0-31.9) weeks and birth weight 1230 (680-2020) grams had continuous aEEG during the first postnatal 72-84 hours. aEEG maturity scores and average maximum and minimum amplitudes were evaluated. Conventional brain MRI was performed at 41.2 (37.1-44.1) weeks postmenstrual age on a 3T GE system and scored qualitatively for injury and maturation. **Results:** the average aEEG total maturity score and its cycling subscore were positively and significantly associated with the total MRI maturation score after adjustment for GA, morphine sedation, and postmenstrual age at MRI examination. No association was found between the aEEG measures and the MRI injury scores. **Conclusion:** Early aEEG maturity seems to relate to structural MRI brain maturation at term equivalent age in preterm infants.

INTRODUCTION

Despite improved survival of extremely preterm infants within the last two decades, long term cognitive, motor and behavioral impairment remain a significant burden for preterm born children (1) with the extreme preterm infants being most affected (2). Neuroprotective studies in preterm infants are being conducted to improve long-term outcome (3) and robust biomarkers would help to guide such interventional strategies and to help parental counseling. aEEG is a valuable neurophysiologic diagnostic tool for early continuous bedside monitoring of brain function and its background activity can predict short- and long-term outcome in preterm infants (4). Some aEEG studies have shown that the background activity pattern changes as brain matures (5-8). In addition, early signs of dysmaturity in brain activity have been associated with later neurodevelopmental impairments (9-11). Conventional MRI in recent years has helped to describe both brain maturation and brain lesions and understand the nature of brain injuries in preterm infants. Brain maturation can be evaluated with a simple MRI scoring system (12). It was shown that preterm infants at term equivalent age had delayed brain maturation scores compared to term control infants and this was associated with neurobehavioral outcome in preterm infants (12). However, the correlation between early maturational aEEG pattern and brain maturation on MRI has not been established to date. Hence, the aim of the study was to analyze the association between the findings of these two assessment methods performed at two different periods of early life in preterms infants. We hypothesized that the level of early aEEG tracing maturation could be predictive of later brain structural maturation and injury as measured with conventional MRI at term equivalent age.

RESULTS

Study Subjects

Thirty-nine infants were included in this study with a mean (range) gestational age (GA) of 29.5 (27.0 – 31.9) weeks and birth weight of 1230 (680 – 2020) grams. Perinatal characteristics of the subjects are listed in table 1. No infant suffered from sepsis or necrotizing enterocolitis. aEEG tracings of all infants were evaluated. The aEEG recording began at a median (IQR) age of 13.0 (11.5 – 19.0) hours and was continuously performed until 88.5 (78.75-93.75) hours after birth. MRI was performed at a mean postmenstrual age (PMA) of 41.2 (37.1 – 44.1) weeks. Two infants had intraventricular hemorrhage on early ultrasound imaging of which one required an Omayya reservoir to treat posthemorrhagic ventricular dilatation. No other major ultrasound lesions were seen.

Early aEEG Measurements

Average aEEG total maturity score and cycling subscore over the first 3-4 days of life of all 39 infants correlated positively with GA ($r = 0.70$ and 0.69 , respectively; both $p < 0.001$), and negatively with morphine sedation ($r = -0.49$ and -0.43 ; $p = 0.001$ and 0.007 , respectively). No other significant correlation was found between aEEG scores and perinatal data. Average aEEG maximum amplitude correlated positively with GA ($r = 0.35$, $p = 0.027$) and negatively with morphine sedation ($r = -0.35$, $p = 0.031$), while average minimum aEEG amplitude did not correlate with any perinatal data. Values of each aEEG measure tended to increase over the monitoring time. The median (interquartile range) slopes were 0.33 ($0.03 - 0.73$) for the total maturity score, 0.29 ($0 - 0.78$) for the cycling subscore, 0.39 ($-0.27 - 0.80$) for the maximum aEEG amplitude, and 0.70 ($0.60 - 0.78$) for the minimum aEEG amplitude (all $p < 0.001$).

In retrospect, at the offline analysis of the aEEG tracing, one infant with normal cranial ultrasound examination had two brief (2 and 3 minutes respectively) periods

of suspected electrical seizure activity in the left hemisphere during the 2nd and the 26th hour of life. No abnormal movement was noted, no standard EEG was done nor has any treatment been given at that time.

Conventional MRI at Term Equivalent Age

Seven (18%) infants had no white matter abnormalities (scores 5-6), 22 (56%) had mild white matter abnormalities (scores 7 – 9), and ten (26%) had moderate white matter abnormalities (scores 10 – 12). None had severe white matter abnormalities. All infants had grey matter scores between 3 and 5 reflecting normal grey matter. No correlation was found between injury scores and GA at birth. Two infants had punctate hemorrhagic cerebellar lesions. Quality of gyral maturation (grey matter injury subscore) was negatively correlated with PMA ($r = -0.36$, $p = .02$). There were no other significant correlations between PMA and injury scores. Total maturation score (TMS) ranged between 9 and 15. TMS correlated significantly with PMA ($r = 0.55$, $p < .01$) (Figure 1) but not with GA at birth. Figures 2 and 3 show two examples of qualitative low- and high scored conventional MRI study, respectively.

Relation between Early aEEG and MRI at Term Equivalent

Table 2 shows the Spearman rank's correlation coefficients between the aEEG and MRI scores. A significant positive correlation between the average aEEG total maturity score, cycling subscore, as well as the maximum aEEG amplitude over the first 3 days of life, and the MRI TMS at term equivalent age was found. Among all MRI maturation subscores, the cortical folding correlated moderately with both the aEEG total maturity score, its cycling subscore, and weakly with the minimum aEEG amplitude. The MRI subscores germinal matrix and bands of migrating glial cells correlated positively with the aEEG total maturation score and the average minimum

aEEG amplitude, and with the average maximum aEEG amplitude. We found that no aEEG measure did correlate with the MRI lesion scores in all study infants. The slopes of the different aEEG measurement series did not correlate with any of the MRI scores. In the multivariate linear regression analyses the aEEG total maturity score and the cycling subscore were positively associated with the MRI total maturity score. For every unit increase of aEEG total maturity score and cycling subscore there was an increase of 0.48, 0.39 unit of MRI total maturity score and cycling score, respectively, 48% and 45% of variance explained. These relationships were adjusted for GA, morphine sedation during aEEG monitoring, and PMA at MRI exam. In the subgroup of patients with no sedation ($n = 32$), the aEEG total maturity score was significantly associated ($\beta = 0.21$, $p < .04$) and the cycling subscore tended to be associated ($\beta = 0.52$, $p = .05$) with the MRI total maturity score. Both in the subgroup ventilated ($n = 9$) and non-ventilated infants ($n = 30$) significant associations between the aEEG total maturity score ($\beta = 0.21$, $p < .04$ and $\beta = 1.15$, $p < .04$, respectively) or its cycling subscore ($\beta = 0.56$, $p < .05$ and $\beta = 5.82$, $p < .02$, respectively) and the MRI total maturity score were found. Table 3 shows the results of the 4 models calculated for each aEEG measure, after correction for GA, morphine sedation during aEEG monitoring and PMA at MRI exam.

DISCUSSION

The results of our study show that aEEG monitoring in preterm infants early after birth may be predictive for brain maturation on conventional MRI performed at term equivalent age. That confirms our hypothesis of a correlation between neurophysiological maturity, measured early after birth, and structural brain maturity assessed at term equivalent age. The early detection of brain dysmaturity provides the clinicians with an instrument to identify preterm infants at risk for abnormal

cortical development and for unfavorable neurodevelopmental outcome (13). This would enable to implement targeted neuroprotective intervention in order to prevent subsequent impairment. The role of early aEEG as possible biomarker for structural brain maturation however needs to be further evaluated in a study with a larger cohort in order to define cut-offs points for aEEG measures and to assess the range of MRI TMS for specific gestational ages. Among all MRI parameters, the score for cortical folding, so gyrification and cortical maturation at term equivalent age correlated best with early aEEG measures. The findings of the present study are consistent with work by Buchmann et al. showing slow-wave EEG activity as a marker for cortical maturation in normal adolescents (14). In preterm infants (<30 weeks of GA at birth without brain lesions on MRI), Biagioni et al. showed a positive correlation between maturational EEG features and cortical folding and PMA studied soon after birth. However, no independent correlate of global cortical maturity on EEG parameters was found since PMA had a strong influence on both anatomical and electrophysiological maturation (15). In contrast to their study where both EEG and MRI were done soon after birth, in the present study early aEEG was correlated with late MRI at term equivalent age showing a correlation between early aEEG measures and cortical folding adjusted for PMA. A study using auditory event-related potentials showed that an earlier right neurophysiological maturation was paralleled by an ipsilateral structural development seen on MR in preterm infants (16). Interestingly, in a study on early cortical folding, increased gyrification was associated with more mature behavioral function at term equivalent age (17). To what extent early cortical electrical activity as measured by aEEG can induce structural cortical maturation cannot be determined by this study and would require serial MRI.

Many MRI studies at term equivalent age have shown that cortical development is delayed in preterm infants (18-20). Interestingly, the total white matter and grey matter injury score on MRI at term equivalent age did not correlate with any early aEEG measure. The total injury score was derived from composite white and grey matter scores. Even when the individual white or grey matter scores were correlated with early aEEG measures, no significant correlations were found. However, this might not be surprising as most of the infants in this cohort had mild to moderate white matter injury and none had abnormal grey matter injury scores. This narrow range of abnormalities could explain the lack of correlation between early aEEG measures and MRI injury score. Also the MRI injury scores are mainly focused on white matter abnormalities and not cortical abnormalities. Visual assessment of cortical abnormalities is difficult and perhaps a more objective quantitative volumetric assessment of the cortex would show additional correlation between early aEEG measures and cortical abnormalities. Several studies showed that aEEG background activity can indicate large intracerebral hemorrhage (10, 11, 21-24) or cystic periventricular leukomalacia in preterm infants (25). Although we had a narrow range of mild to moderate brain abnormalities defined by the Woodward score, one could expect a correlation between presence of injury on MRI and aEEG measures. However, this was not the case probably because of localization and timing of the aEEG monitoring. In fact this could be because in the present study a 2-channel aEEG device was used with electrodes being placed in the C3, P3 and C4 and P4; and this setting obviously does not cover all cortical regions and therefore might miss regional cortical activity alterations. Alternatively, brain injury could have been not detected by electrophysiological monitoring because the insult or evolution of injury occurred after the first three days after birth, hence after the aEEG monitoring period. Indeed, it has been reported that events such as for example postnatal infection (26)

or chronic lung disease (27) influence brain maturation. Hence, it is likely that if serial aEEG monitoring until term equivalent age would have been performed a correlation with brain injury on MRI at term equivalent age would have been seen.

Some limitations of this study have to be mentioned. Continuous aEEG measures cortical activity through two parieto-central channels only, a limited sector of cortex can therefore be monitored. It may be that we missed regional brain dysfunction. However this method enabled us to monitor the newborns continuously during many days after birth, which is impracticable with a multichannel EEG device. Additionally, in our study the assessment of the electrocortical maturity as well as the outcome measure were based on the semiquantitative aEEG- and MRI assessment, respectively, which could be subjected to bias. However, we used two validated assessment methods and we reached good interobserver agreement levels. Another important limitation of the present work is the relatively small sample size, which limits the power of the statistical analysis. The wide GA range and the lack of extremely immature preterms in the study group do not allow a generalization of our findings to preterm newborns with GA below 27 weeks. Further research with larger numbers, including more immature preterms, serial MRI and focus on the long-term neurodevelopment of these infants will be needed.

CONCLUSION

In conclusion, the results of this study indicate that early quantitative aEEG measures in preterm infants seem to correlate with brain maturation on MRI at term equivalent age. This implies that early aEEG monitoring could play a role for assessment of later cortical maturation. These results are important as they show a good correlation between functional and structural brain maturation.

MATERIALS AND METHODS

The institutional ethics boards of the University Children's Hospital Zurich and of the Canton of Zurich approved the study protocol. Informed consent was obtained from the parents.

Subjects

This is a prospective observational study including inborn preterm infants born below 32 weeks who were admitted to the neonatal intensive care unit of Zurich University Hospital between January 2009 and May 2011. Infants who had both, early aEEG monitoring and MRI at term equivalent age were eligible for the study. Exclusion criteria were chromosomal and/or congenital anomalies, central nervous system infection or metabolic disorders. GA was assigned based on the best obstetrical estimate, on the last menstrual cycle and prenatal ultrasonography scans. Small doses of intravenous morphine-sedation (maximum 12 microgram/kg/hour) during aEEG monitoring were not considered as exclusion criteria for the analysis. aEEG sequences of infants with other sedative medication were excluded from the analysis. Each infant had serial cranial ultrasound examinations at day 1, 3, 7 after birth and weekly or every two weeks, as clinically indicated, until discharge.

Amplitude-integrated Electroencephalography

Two-channel aEEG monitoring with a Brainz BRM3 monitor (Natus Medical Incorporated, San Carlos, CA) was recorded from biparietal hydrogel electrodes, corresponding to C3, P3 and C4, P4, according to the international electroencephalogram classification 10-20 system, ground F_z (28). The reference electrode was placed on the right or left shoulder. The technique and the physiologic basis of the aEEG have been outlined in detail elsewhere (29). The raw EEG signal

is amplified and filtered attenuating the activity $<2\text{Hz}$ and $>15\text{Hz}$, and its amplitude is semilogarithmic integrated, rectified and time compressed (1h/6cm of recording-display scale). Duration of the aEEG monitoring lasted from the 1st to the 3rd day of life. For pattern analysis aEEG tracings were divided in epochs of 3 hours each. Only tracings with impedance below 12 kOhm were analyzed. Tracing epochs with either suspect seizure events or artifacts were excluded from the analysis. Cross-cerebral P3–P4 aEEG records were analyzed. One observer (GN) experienced in aEEG interpretation performed the visual assessments of aEEG off-line based on a previously published score as follows below and these scores were used for statistical analysis. Visual analysis was performed blinded to quantitative analysis of the aEEG, neonatal outcome, and MRI findings. A second observer (CH) analyzed aEEG tracings of 10 infants only for inter-observer agreement testing.

Visual aEEG Analysis

Visual semiquantitative aEEG analysis was performed according to the scoring system for the evaluation of brain maturity as suggested by Burdjalov and associates (5). Four aEEG pattern components including: continuity; cycling; amplitude of the lower border of the aEEG traces, which was visually estimated as the average lower microvolt level during the recording periods; and aEEG bandwidth, which refers to a combination of the voltage span (peak-to-trough) of the tracing and the amplitude of the lower aEEG border. For each 3-hours artifacts free aEEG epoch components' subscores were summed to obtain a total maturity score, ranging 0 to 13, the lower the score the more immature the brain activity. Subscores for cycling, ranging 0 to 5, were analyzed separately. Cohen's kappa (95% CI) for inter-rater agreement was 0.79 (0.75-0.82) for the total maturity score and 0.60 (0.52-0.66) for the cycling subscore, respectively.

Quantitative aEEG Analysis

Quantitative automated analysis of the aEEG tracings was performed using the BrainZ Analyze Research software (*Chart analyser 1.71, The Liggins Institute, Auckland, NZ*). Raw aEEG data were exported and 1-minute average values for the maximum and minimum amplitudes of each aEEG epochs were calculated (30). Maximum and minimum aEEG amplitude corresponds to the upper and lower border of the aEEG envelope, respectively.

MRI Data Acquisition and Analysis Procedure

The MRI protocol included the following imaging sequences: axial T2 weighted images FSE (TE 102 ms, TR 5640, ETL 24, FOV 18 x 14.4, matrix 512 x 320, slice thickness 2.5 mm, gap = 0.5 mm, 2 NEX), 3D T1 weighted images (TE 2.6 ms, TR 5.7, TI 750 ms, flip angle 12 degrees, FOV 18 cm x 18 cm, matrix 224x224, slice thickness 1.4 mm, gap 0, 1 NEX), Proton density T2 FSE (TE 26, 128 ms, TR 6600, ETL 16, FOV 18 x 13.5 cm, matrix 256 x 192, slice thickness 1.5 mm, gap 0, 2 NEX) and sagittal T2 weighted images FSE (TE 102, TR 3900, ETL 24, FOV 18 cm x 18 cm, slice thickness 3 mm, gap 0, matrix 384 x 320, 1 NEX). Cerebral structural maturation was assessed (CH) according to a previously published protocol (31). The degree and localization of myelination, cortical folding, the presence and distribution of the germinal matrix and the bands of migrating glial cells were scored separately. The MRI TMS was calculated as the sum of the four separate scores with range 4 to 21, the higher the score the higher the brain maturation. T1 and T2 weighted images were assessed (CH) for injury according to a previously published scoring system by Woodward et al. (32). A total injury score and subscores for grey and white matter injury were calculated. Scores of 5 to 6 reflect no white matter abnormality, 7 to 9

mild, 10 to 12 moderate and 13 to 15 severe white matter abnormality. Grey matter scores of 3 to 5 reflect normal and scores of 6 to 9 abnormal grey matter. Cohen's kappa for inter-rater agreement (data of 20 infants assessed by a second observer, RHL) was (95% CI) 0.59 (0.37-0.81) for the TMS and 0.77 (0.61-0.92) for the injury score, respectively.

Statistics

Means (SD) of all epoch's values were calculated for each subject and all aEEG measures. The slope of the development of each aEEG measure over the monitoring time was computed by a linear regression model for all subjects and averaged. For testing the correlation between aEEG measurements and MRI scores the Spearman's Rank correlation coefficients were calculated. In a second step, the following perinatal variables were tested for their association with aEEG measurements: GA, PMA, morphine sedation, caffeine- and indomethacin administration, arterial cord pH, 5 minutes Apgar score, CRIB score, intraventricular hemorrhage greater than grade II after Papile (33) and cystic periventricular leukomalacia. In a third step, aiming at analyzing an adjusted association between aEEG measures and MRI scores, a multivariate linear regression analysis was performed, where variables which were significantly associated with the aEEG and MRI scores were entered (GA, PMA, sedation). Two-sided tests were used throughout, and a p-value < 0.05 was considered significant. SPSS 18.0 software (SPSS Inc., Chicago, IL) was used.

ACKNOWLEDGEMENTS

We gratefully thank all children and their parents who participated in this study.

REFERENCES

1. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* 2007;196:147.e141-148.
2. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and Developmental Disability After Extremely Preterm Birth. EPICure study group. *The N Eng J Med* 2000;343:378-384.
3. Fauchère JC, Dame C, Vonthein R, et al. An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. *Pediatrics* 2008;122:375-382.
4. Hellström-Westas L, Rosén I. Continuous brain-function monitoring: State of the art in clinical practice. *Sem Fetal Neonatal Med* 2006;11:503-511.
5. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics* 2003;112:855-861.
6. Olischar M, Klebermass K, Kuhle S, et al. Reference values for amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks' gestational age. *Pediatrics* 2004;113:e61-e66.
7. Sisman J, Campbell DE, Brion LP. Amplitude-integrated EEG in preterm infants: maturation of background pattern and amplitude voltage with postmenstrual age and gestational age. *J Perinatol* 2005;25:391-396.
8. Niemarkt HJ, Andriessen P, Peters CH, et al. Quantitative analysis of amplitude-integrated electroencephalogram patterns in stable preterm infants, with normal neurological development at one year. *Neonatology* 2010;97:175-182.

9. Okumura A, Hayakawa M, Oshiro M, Hayakawa F, Shimizu T, Watanabe K. Nutritional state, maturational delay on electroencephalogram, and developmental outcome in extremely low birth weight infants. *Brain Dev* 2010;32:613-618.
10. Chalak LF, Sikes NC, Mason MJ, Kaiser JR. Low-voltage aEEG as predictor of intracranial hemorrhage in preterm infants. *Pediatr Neurol* 2011;44:364-369.
11. Bowen JR, Paradisis M, Shah D. Decreased aEEG continuity and baseline variability in the first 48 hours of life associated with poor short-term outcome in neonates born before 29 weeks gestation. *Pediatr Res* 2010;67:538–544.
12. Hüppi PS, Schuknecht B, Boesch C, et al. Structural and neurobehavioral delay in postnatal brain development of preterm infants. *Pediatr Res* 1996;39:895-901.
13. Scher MS. Neurophysiological assessment of brain function and maturation. II. A measure of brain dysmaturity in healthy preterm neonates. *Pediatr Neurol* 1997;16:287-295.
14. Buchmann A, Ringli M, Kurth S, et al. EEG sleep slow-wave activity as a mirror of cortical maturation. *Cereb Cortex* 2011;21:607-615.
15. Biagioni E, Frisone MF, Laroche S, et al. Maturation of cerebral electrical activity and development of cortical folding in young very preterm infants. *Clin Neurophysiol* 2007;118:53-59.
16. Mento G, Suppiej A, Altoè G, Bisiacchi PS. Functional hemispheric asymmetries in humans: electrophysiological evidence from preterm infants. *Eur J Neurosci* 2010;31:565-574.
17. Dubois J, Benders M, Borradori-Tolsa C, et al. Primary cortical folding in the human newborn: an early marker of later functional development. *Brain Dev* 200;131:2028-2041.

18. Ajayi-Obe M, Saeed N, Cowan FM, Rutherford MA, Edwards AD. Reduced development of cerebral cortex in extremely preterm infants. *Lancet* 2000;356:1162-1163.
19. Kapellou O, Counsell SJ, Kennea N, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;3:e265.
20. Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. *Lancet Neurol* 2009;11:1042-1055.
21. Greisen G, Hellström-Westas L, Lou H, Rosén I, Svenningsen NW. EEG depression and germinal layer haemorrhage in the newborn. *Acta Paediatr Scand* 1987;76:519-525.
22. Hellström-Westas L, Klette H, Thorngren-Jerneck K, Rosen I. Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages. *Neuropediatrics* 2001;32:319-324.
23. Olischar M, Klebermass K, Waldhoer T, Pollak A, Weninger M. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr* 2007;96:1743-1750.
24. Kidokoro H, Kubota T, Hayashi N, et al. Absent cyclicity on aEEG within the first 24 h is associated with brain damage in preterm infants. *Neuropediatrics* 2011;41:241-245.
25. Kato T, Okumura A, Hayakawa F, Tsuji T, Natsume J, Hayakawa M. Amplitude-integrated electroencephalography in preterm infants with cystic periventricular leukomalacia. *Early Hum Dev* 2011;87:217-221.

26. Chau V, Brant R, Poskitt KJ, Tam EW, Synnes A, Miller SP. Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. *Pediatr Res* 2012;71:274-279.
27. Ball G, Counsell SJ, Anjari M, et al. An optimised tract-based spatial statistics protocol for neonates: applications to prematurity and chronic lung disease. *Neuroimage* 2010;53:94-102.
28. van Rooij LG, de Vries LS, Handryastuti S, et al. Neurodevelopmental outcome in term infants with status epilepticus detected with amplitude-integrated electroencephalography. *Pediatrics* 2007;120:e354-363.
29. Rosén I. The physiological basis for continuous electroencephalogram monitoring in the neonate. *Clin Perinatol* 2006;33:593-611.
30. West CR, Harding JE, Williams CE, Gunning MI, Battin MR. Quantitative electroencephalographic patterns in normal preterm infants over the first week after birth. *Early Hum Dev* 2006;82:43-51.
31. Childs AM, Ramenghi LA, Cornette L, Tet al. Cerebral maturation in premature infants: quantitative assessment using MR imaging. *Am J Neuroradiol* 2001;22:1577-1582.
32. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006;355:685-694.
33. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. *J Pediatr* 1978;92:529-534.

FIGURE LEGENDS

Figure 1

Caption:

Spearman correlation between postmenstrual weeks at MRI examination and total maturation score in the study group ($r = 0.55$; $p < .01$).

Figure 2

Title:

- a) Day 1
- b) Day 3
- c) At term equivalent

Caption:

Development over time of the aEEG background between day 1 and 3 after birth in preterm newborn of 27 5/7 weeks of gestation: (a) prevalently burst suppression aEEG background pattern at day 1 after birth with total maturity score 2; (b) progressively discontinuous aEEG background pattern with variable minimum aEEG amplitude below 5 μ Volts and total maturity score 2; and c) axial T2 weighted MR image at 38 0/7 weeks PMA; Scores: germinal matrix 3, cortical folding 2, myelination 2, bands of migration 2, total maturation score 9.

Figure 3

Title:

- a) Day 1
- b) Day 3
- c) At term equivalent

Caption:

Development over time of the aEEG background between day 1 and 3 after birth in preterm newborn of 27 4/7 weeks of gestation: (a) prevalently discontinuous aEEG background pattern at day 1 after birth with total maturity score 6; (b) progressively continuous aEEG background with more mature cycling activity and total maturity score 8; and c) axial T2 weighted MR image scanned at 41 0/7 weeks PMA. Scores: germinal matrix 4, cortical folding 3, myelination 2, bands of migration 4, total maturation score 14.

Figures

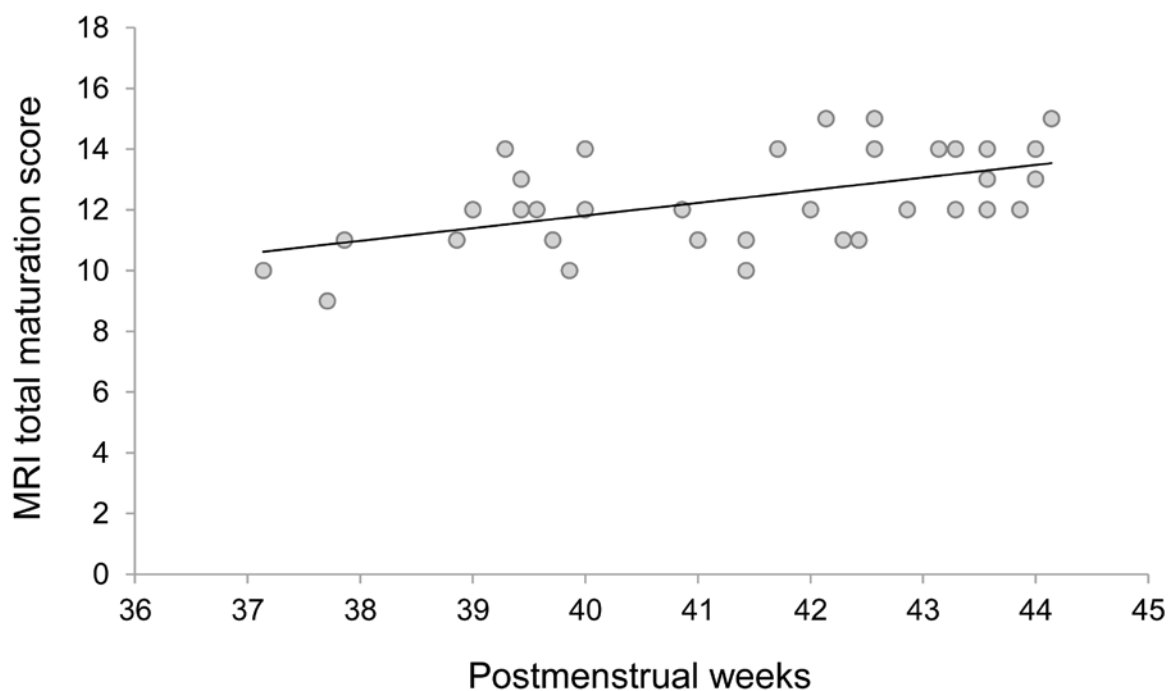


Figure 1. Spearman correlation between postmenstrual age at MRI examination and total maturation score in the study group ($r = 0.55$; $P < 0.01$). MRI, magnetic resonance imaging.

Figure 2

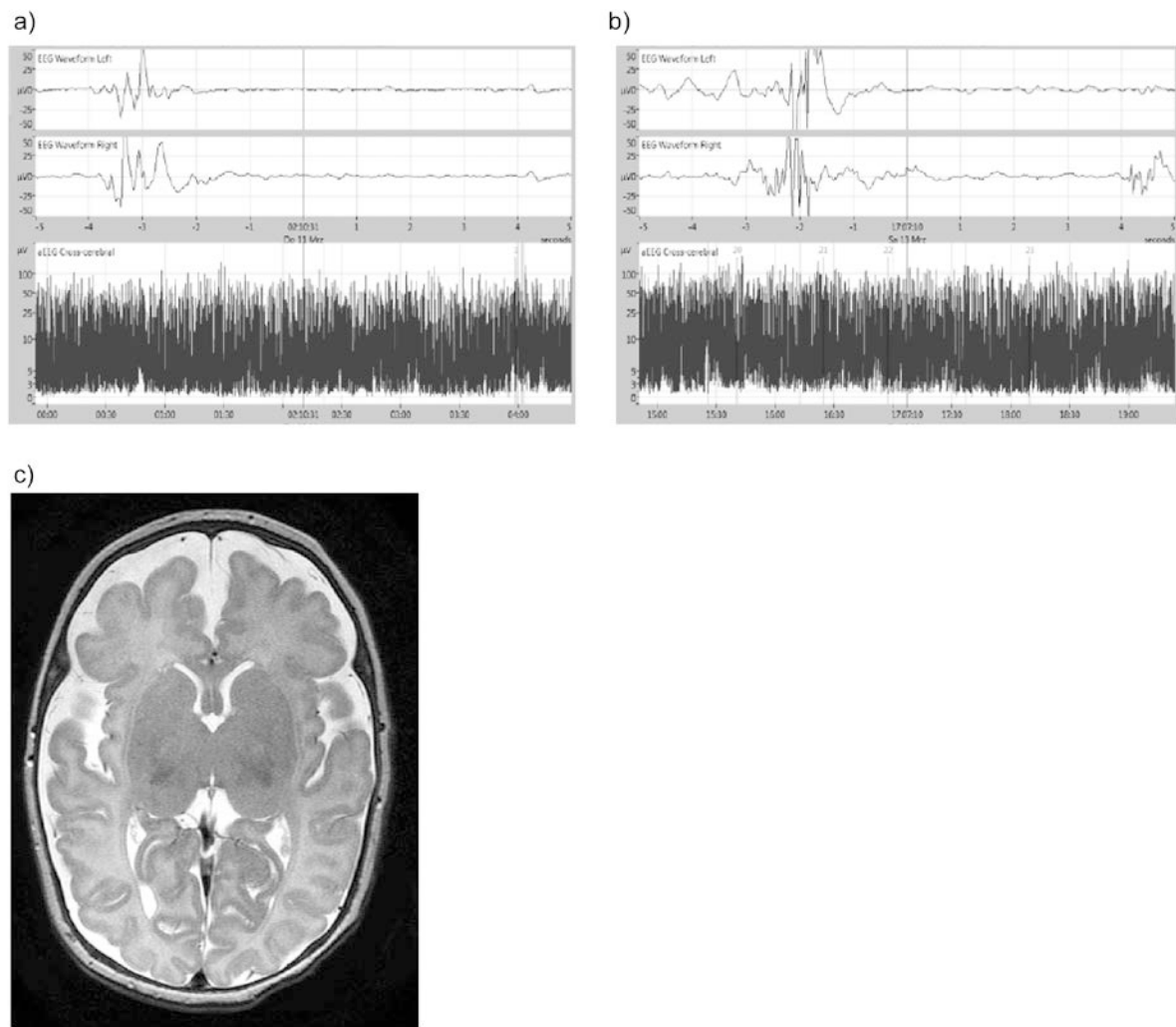


Figure 2. Development over time of the aEEG background between days 1 and 3 after birth in a preterm newborn of 27 5/7 wk of gestation.

(a) Prevalently burst suppression aEEG background pattern at day 1 after birth with total maturity score 2.

(b) Progressively discontinuous aEEG background pattern with variable minimum aEEG amplitude below 5 μ V and total maturity score 2.

(c) Axial T2-weighted MRI scanned at 38 0/7 wk PMA. Scores: germinal matrix: 3, cortical folding: 2, myelination: 2, bands of migration: 2, and total maturation score: 9.

(a) Day 1; (b) day 3; and (c) at term-equivalent age. aEEG, amplitude-integrated electroencephalogram; MRI, magnetic resonance imaging; PMA, postmenstrual age.

Figure 3

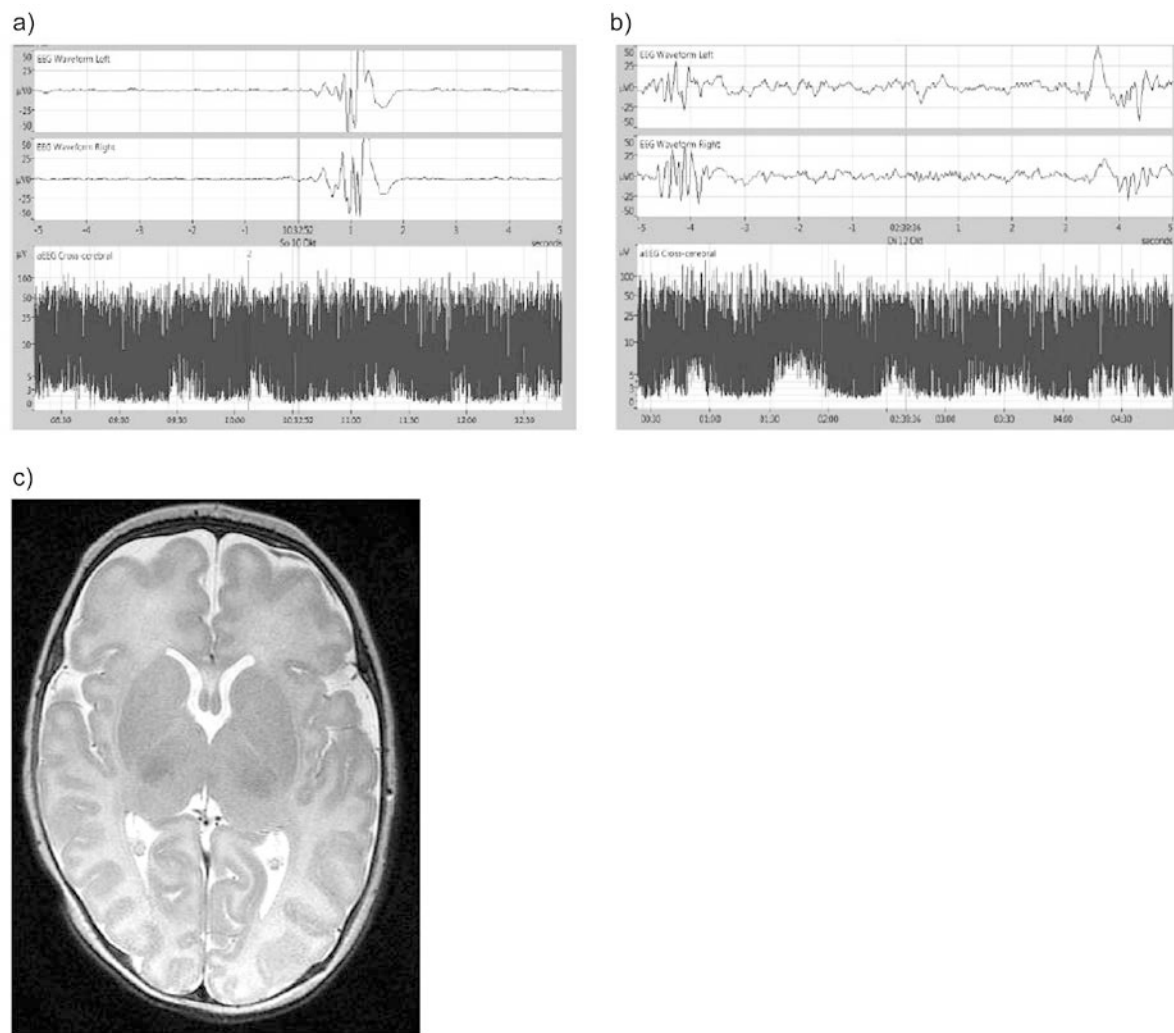


Figure 3. Development over time of the aEEG background between days 1 and 3 after birth in a preterm newborn of 27 4/7 wk of gestation.

(a) Prevalently discontinuous aEEG background pattern at day 1 after birth with total maturity score 6.

(b) Progressively continuous aEEG background with more mature cycling activity and total maturity score 8.

(c) Axial T2-weighted MRI scanned at 41 0/7 wk PMA. Scores: germinal matrix: 4, cortical folding: 3, myelination: 2, bands of migration: 4, and total maturation score: 14.

(a) Day 1; (b) day 3; and (c) at term-equivalent age. aEEG, amplitudeintegrated electroencephalogram; MRI, magnetic resonance imaging; PMA, postmenstrual age. Text

Tables

Table 1: Perinatal characteristics of the study infants.

Perinatal variables	n = 39
Gestational age (weeks) m (SD; range)	29.5 (1.4; 27.0 – 31.9)
Birth weight (grams) m (SD; range)	1230 (330; 680 - 2020)
SGA, n (%)	6 (15)
Sex/Male, n (%)	19 (49)
Pre-eclampsia, n (%)	9 (23)
Chorioamnionitis/Funisitis, n (%)	9 (23)
Antenatal corticosteroids, n (%)^a	34 (87)
Cesarean section, n (%)	39 (100)
Arterial Cord pH, m (SD)	7.32 (0.1)
5' Apgar, m (SD)	7.1 (2.1)
Days on artificial ventilation, M (IQR)	0 (0 – 1)
CRIB score, M (IQR)	1 (1 – 4)
Respiratory distress, n (%)	39 (100)
Surfactant, n (%)	13 (33)
Sedation while aEEG, n (%)	7 (18)
Caffeine^b, n (%)	9 (23)
Indomethacine^c, n (%)	14 (36)

aEEG, amplitude-integrated electroencephalogram; CRIB, clinical risk index for babies;

IQR, interquartile range; M, median; SGA, small for gestational age, defined as the birth weight <10 centile.

aThree infants (8%) did not receive any and two infants (5%) received incomplete antenatal steroids (i.e., one of two doses of 12-mg betamethasone given intramuscularly within 24 h before delivery). bFirst bolus of 20 mg/kg intravenous or arterial, from the median (range) 47th (27th–69th) hour of life and further daily administration of 5 mg/kg/d. cSix doses of 0.1 mg/kg/d (n = 8) or three doses of 0.2 mg/kg/12 h (n = 6) intravenous from the 63rd (54th–72nd) hour of life.

Table 2

Spearman correlation coefficients between aEEG measurements and MRI maturation and injury scores.

	MRI maturational score					MRI injury score		
	Total	Myelination	Cortical folding	Germinal matrix	Bands of migrating glial cells	WM injury	GM injury	PWML
Total maturity score after Burdjalov et al. (5)	0.44 **	0.21	0.42 **	0.34 *	0.30	0.16	- 0.05	0.06
Cycling subscore after Burdjalov et al. (5)	0.41 **	0.20	0.45 **	0.26	0.30	0.18	- 0.05	0.05
Maximal aEEG amplitude	0.42 **	0.27	0.13	0.29	0.34 *	- 0.22	- 0.25	0.17
Minimum aEEG amplitude	0.26	0.23	0.34 *	0.39 *	- 0.00	- 0.22	0.04	- 0.28

aEEG, amplitude-integrated electroencephalogram; GM, gray matter; MRI, magnetic resonance imaging; PWML, punctate white matter lesion; WM, white matter.

*P < 0.05. **P < 0.01.

Table 3

Summary of multiple regression analyses for aEEG predictors of anatomical brain maturation assessed at term age equivalent by conventional MRI in preterm infants.

		Multivariate linear regression				
		MRI maturation total score adjusted for GA, morphine sedation^a and PMA				
Equation	aEEG measurements	β	SE	95% - CI	% Variance explained	p-value
1	Total maturity score after Burdjalov et al.	0.48	0.10	0.54 – 0.44	48	.014
2	Cycling subscore after Burdjalov et al.	0.39	0.26	0.31 – 1.09	45	.039
3	Maximal aEEG amplitude	0.27	0.05	- 0.01 – 0.19	44	.067
4	Minimal aEEG amplitude	0.16	0.10	- 0.10 – 0.31	40	.313

Equation 1: F = 7.89; P < 0.001; R² = 0.48; R² adjusted = 0.42. Equation 2: F = 7.04; P < 0.001; R² = 0.45; R² adjusted = 0.39.

Equation 3: F = 6.62; P < 0.001; R² = 0.44; R² adjusted = 0.37.

Equation 4: F = 5.61; P = 0.001; R² = 0.40; R² adjusted = 0.33.

aEEG, amplitude-integrated electroencephalogram; β, change in score or amplitude for 1-unit increase in MRI maturation score; CI, confidence interval; GA, gestational age;

MRI, magnetic resonance imaging; PMA, postmenstrual age; SE, standard error of the regression coefficient.

aMorphine sedation during aEEG monitoring (maximum 12 mg/kg/h endovenous).